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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/605,283	09/19/2003	Kapil N. Bhalla	1372.76.PRC	2282

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EXAMINER
JAGOE, DONNA A

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
08/18/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/605,283	**Applicant(s)** BHALLA ET AL.	
	Examiner Donna Jagoe	**Art Unit** 1619	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 08 July 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *19,23,26 and 27*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

/D. J./
Examiner, Art Unit 1619

1.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant asserts that Theising does not teach supplementing STI571 with SAHA and VCU does not teach the combination of SAHA with STI571. In response, as stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art. Applicant asserts that "not every agent used to treat leukemia can be combined with every other agent that is used to treat leukemia and states that the state of the art at the time of the invention was that it was not known if cancer therapeutics could be combined to enhance their effects and further states that Theising illustrates this by stating on page 3198 that the possibility of antagonism between STI571 and antileukemic agents was a major reason for undertaking the studies. In response, Theising teaches resistance would develop with long-term administration of STI571 and suggest the combination of STI571 with other agents to either prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone (page 3199, columns 1-2). In both ALL and CML, Thiesing et al. teach that STI571 should be supplemented with another agent known to treat leukemia. Applicant further recites the mechanism of action of the agents tested with Theising et al., however, Theising does not state any specific mechanism of action when it states that "resistance would develop with long-term administration of STI571" and suggest the combination of STI571 with other agents to either prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone. In response to allegations that not all antileukemic agents performed and specifically, the combination of HU and STI571 was antagonistic, Theising states that the combination of STI571 with HU also demonstrated significant inhibition of colony formation with MO7p210 and K562 cell line assays (page 3198, column 1), thus this combination was successful with two of the three cell lines tested. In response to arguments that the cells examined in VCU were not imatinib mesylate refractory cells nor were they CML or ALL cells. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Both references teach treatment of resistant leukemia and teach treatment with STI571 (Thiesing et al.) and SAHA (VCU) in the treatment of leukemia. Applicant asserts that Thiesing does not teach supplementing STI571 with SAHA and VCU teaches administration of cyclin dependent kinase inhibitors with cellular differentiation agents to promote apoptosis in cancer cells and further asserts that instant claim 19 is drawn to the administration of imatinib mesylate and SAHA. In response, one having ordinary skill in the art could have combined SAHA and imatinib mesylate as claimed for the treatment of leukemia and in combination, each element would have performed the same function as it did separately and the results would have been predictable. Thus, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to have administered SAHA in combination with imatinib mesylate, as taught by both Thiesing et al. and VCU. One would have been motivated to do so because each of the therapeutic agents has been individually taught in the prior art to be successful at treating leukemia. Moreover, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the very same purpose. The idea of combining them flows logically from having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering the combination one would achieve a method for treating CML. Applicant argues that the cyclin dependent kinases of VCU "oppose" apoptosis. In response, VCU teach that one agent alone (FP alone) had a minimal effect on apoptosis (see page 33, line 27 to page 34, line 3) and that the co-administration of a cyclin dependent kinase and a cellular differentiation agent (PMA and FP) resulted in a synergistic drug interaction (page 15, lines 16-21). It further teaches that its method involves co-administering to the cancer cells a cyclin dependent kinase inhibitor and an agent that induces cellular differentiation. Several categories of agents that induce cellular differentiation may be utilized in the invention, including histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA). Examples of types of cancer cells in which apoptosis may be promoted by the invention are leukemia ceils, prostate cancer cells, breast cancer cells, multiple myeloma cells, and lymphoma cells (page 4, line 27 to page 5, line 9). Applicant states that claim 23 further recites that the cells are "exposed" to imatinib mesylate and SAHA for about 48 hours and states that the prior art does not address this limitation. In response, the instant specification teaches that the process of "contacting" the target cells is accomplished by "administering" a tyrosine kinase inhibitor and a histone deacetylase inhibitor to the subject (paragraph11). In the prior art, for both ALL and CML, Thiesing et al. teach administration of the tyrosine kinase inhibitor tyrosine kinase inhibitor, imatinib mesylate or STI571 and teach that it should be supplemented with another agent known to treat leukemia. Thiesing et al. does not teach supplementing STI571 with suberoylanilide hydroxamic acid. VCU teach administration of a histone deacetylase inhibitor with another agent known to treat leukemia and teach co-administration within the time range of 24-72 hours (page 11, lines 7-12) which overlaps and encompasses the claimed 48 hours. Applicant further asserts that the prior art does not teach a further limitation in that cancer cells are CML cells that are either accelerated phase or blast crisis phase. In response, Thiesing et al. teach that STI571 (imatinib mesylate) has shown significant activity in all phases of CML as well as Philadelphia chromosome positive acute leukemias (ALL) (also known as blast crisis phase) (page 3195, 1st paragraph). Additionally, VCU teach co-administration a cellular differentiation agent (such as SAHA) to promote apoptosis in cancer cells in combination with another agent to treat leukemia, such as a cyclin dependent kinase inhibitor (see abstract).